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(54) **N-alkylamides of D,L and L(-)-carnitine having antibacterial activity, process for their preparation and pharmaceutical and cosmetic compositions containing same.**

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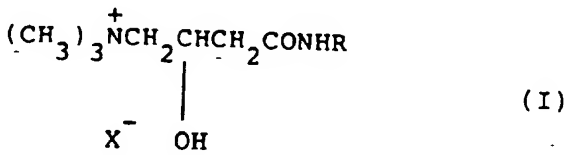
Description

The present invention relates to novel N-alkylamides of D,L and L(-)-carnitine endowed with antibacterial activity, having general formula (I)



(I)

wherein :

X^- is OH^- or the anion of a pharmacologically acceptable acid, and

R is a straight C_{10}-C_{16} alkyl radical.

Preferably, X^- is Cl^-.

The present invention also relates to a process for producing N-alkylamides of formula (I) and the pharmaceutical and cosmetic compositions comprising an amount of at least one of the N-alkylamides (I) suitable for promoting an effective antibacterial action.

Some carnitine N-alkylamides are known already.

In Japanese patent 408435 filed October 31, 1960 in the name of Takeda Chemical Industries, Ltd. carnitinamides structurally analogous to those of formula (I) are disclosed, wherein, however, the radical R is lower alkyl (methyl and ethyl). This Japanese patent discloses that such amides "promote the intestinal peristalsis and are useful as medicaments for intestinal disorders". These amides are prepared by condensing at room temperature a reactive carnitine derivative (an acid halogenide, ester or anhydride) with methylamine or ethylamine.

The N-alkylamides of D,L and L(-)-carnitine according to the present invention are on the other hand prepared via a process which comprises the following two characterizing steps:

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}-C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120-140 °C, for 2-4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture a mixture of D,L or L(-)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of D,L or L(-)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110-130 °C for about 34-38 hours in an atmosphere of inert gas.

After removal under vacuum of the high-boiling solvent, the residue comprising the N-alkylamide (I) is purified and the compound isolated according to known procedures.

The transamination of this process allows the direct conversion of the amide into the N-alkylamides (I) to be carried out. No intermediate steps are needed in order to convert the starting amide in one of those activated compounds (acid halogenides, esters or anhydrides) from which substituted amides are usually obtained (in this regard see the above mentioned Takeda patent). It is apparent that these intermediate steps would lower the yield remarkably and would increase the cost of the end product.

The following non-limiting example illustrates the preparation of one of the N-alkylamides (I) according to the process of this invention.

EXAMPLE

Preparation of D,L-N-dodecylcarnitinamide chloride

A mixture of dodecylamine (25 m moles), ethylene glycol (20.0 grams) and 85% H_3PO_4 (25 m moles) was reacted in a 100-ml round bottom flask, sealed with a rubber stopper, under stirring, at 130 °C for 3 hours under nitrogen.

A mixture of D,L-carnitinamide chloride (50 m moles) and dodecylamine (55 m moles) was then added to the reaction mixture.

The resulting mixture was kept under stirring at 120 °C for 36 hours under nitrogen. When ammonia development ceased, the reaction mixture was cooled and ethylene glycol caused to evaporate at 80 °C under 0.5 mm Hg.

After the residue was dissolved in 80 ml of chloroform, the resulting solution was chromatographed on a silica (50 g) containing column. The product was first eluted with chloroform (100 ml) and with 100 ml of a 9:1 chloroform:isopropanol mixture; then, the product was eluted with 300 ml of a 1:1 chloroform:methanol mixture. The product was recovered by evaporation from the solvent. By further crystallization from 100 ml of tetrahydrofurane and then 100 ml of a 1:1 chloroform:tetrahydrofurane mixture (twice repeated) the title compound was obtained

(Yield: 70%), $[\alpha]_D^{25} = 0$

Elementary analysis:				
C = 62.87%;	H = 11.50%;	N = 7.86%;	Cl = 10.25%	O = 7.52%

Also the remaining N-alkylamides of D,L and L(-)-carnitine chloride encompassed in the general formula (I) were prepared by the same process. In the following table, the main chemico-physical characteristics of the compounds are listed.

$(CH_3)_3\overset{+}{N}CH_2\underset{|}{C}HCH_2CONHR$ Cl^- OH

R	Abbreviated name	Molecular weight	$[\alpha]_D^{25}$	Elementary Analysis Theoretical (%)	Elementary Analysis Found (%)(*)
$C_{10}H_{21}$	L(-) CA-10 DL-CA-10	336.92	-13.62° 0°	C= 60.60 H= 10.77 N= 8.31 Cl= 10.52 O= 9.50	C=60.72 H=10.54 N= 8.85 Cl= 10.00 O= 8.89
$C_{11}H_{23}$	L(-) CA-11 DL-CA-11	350.97	-13.05° 0°	C= 61.60 H= 10.91 N= 7.98 Cl= 10.10 O= 9.12	C= 61.93 H= 11.29 N= 8.05 Cl= 9.80 O= 8.84
$C_{12}H_{25}$	L(-) CA-12 DL-CA-12	364.97	-12.60° 0°	C= 62.53 H= 11.05 N= 7.68 Cl= 9.71 O= 8.77	C= 62.87 H= 11.50 N= 7.86 Cl=10.25 O= 7.52
$C_{13}H_{27}$	L(-) CA-13 DL-CA-13	379.03	-12.23° 0°	C= 63.34 H= 11.17 N= 7.39 Cl= 9.35 O= 8.44	C= 63.65 H= 10.81 N= 7.60 Cl= 9.02 O= 8.92
$C_{14}H_{29}$	L(-) CA-14 DL-CA-14	393.03	-12.01° 0°	C= 64.18 H= 11.28 N= 7.13 Cl= 9.02 O= 6.14	C= 64.94 H= 12.00 N= 7.19 Cl= 9.87 O= 6.00
$C_{15}H_{31}$	L(-) CA-15 DL-CA-15	407.08	-11.62° 0°	C= 64.91 H= 11.39 N= 6.88 Cl= 8.71 O= 7.86	C= 64.99 H= 10.92 N= 6.89 Cl= 8.69 O= 8.51
$C_{16}H_{33}$	L(-) CA-16 DL-CA-16	421.08	-11.08 0°	C= 65.61 H= 11.49 N= 6.65 Cl= 8.42 O= 7.60	C= 64.98 H= 11.87 N= 6.64 Cl= 8.97 O= 7.54

IR spectra

Freq. cm^{-1}	Assignments
950	- OH
1300	- CN -
1470	CH_2 and OH
1560	- NH -
1650	$C(=O)$-NH-
2940	CH
3300	OH

The frequencies and the corresponding assignments can be regarded as identical for all the compounds because the differences between them are not significant.

(*) For both L(-) and DL form the "found" values are substantially identical

TOXICOLOGICAL TESTS

1. Acute toxicity

(1.1) Acute toxicity via the oral route in mice

It was evaluated in albino Swiss mice weighing 20-25 g which had been kept fasting 12 hours before administration.

The compounds dissolved in distilled water were administrated to the animals by gavage.

The animals were divided in groups of 6 animals each and treated with solutions of diminishing concentrations, each concentration being one half of the preceding concentration.

The mice were checked for 7 days following administration in order to verify their possible death or any behavioural alteration.

LD_{50} was evaluated by th Carrol Weil method (Biometrics, Sept. 1952, pages 249-255, "Calculation of median-effective dose").

The results thus obtained are illustrated in table 1 and 1A.

Table 1: Acute Toxicity via the oral route in mice

	DL- CA-10	DL- CA-12	DL- CA-14	DL- CA-16
LD_{50} (mg/kg)	791	1512	1125	1995
Dose (mg/kg)				
4000	-	6/6	6/6	6/6
2000	6/6	5/6	6/6	3/6
1000	3/6	0/6	2/6	0/6
500	0/6	0/6	0/6	0/6
250	0/6	-	-	-

Table 1A : Acute Toxicity via the oral route in mice

	L(-)- CA-10	L(-)- CA-12	L(-)- CA-14	L(-)- CA-16
LD_{50} (mg/kg)	890	1256	1125	1995
Dose (mg/kg)				
4000	-	6/6	6/6	6/6
2000	6/6	6/6	6/6	2/6
1000	4/6	1/6	2/6	1/6
500	0/6	0/6	0/6	0/6
250	0/6	-	-	-

(1.2) Acute toxicity via the intravenous route in mice

It was evaluated in albino Swiss mice weighing 20-25 g.

The animals were injected the compounds dissolved in saline solution, in their caudal vein.

The animals were divided in groups of 6 animals each and treated with solutions of diminishing concentration, each concentration being one half of the preceding concentration. The mice were checked for 48 hours following administration.

LD_{50} was evaluated by the Carrol Weil method.
The results are illustrated in table 2 and 2A.

Table 2: Acute Toxicity via the intravenous route in mice

LD_{50} (mg/kg)	DL- CA-10	DL- CA-12	DL- CA-14	DL- CA-16
	28.28	25.2	48.72	63.33
Dose (mg/kg)				
160	-	-	6/6	6/6
80	6/6	6/6	6/6	6/6
40	5/6	6/6	3/6	2/6
20	1/6	1/6	0/6	0/6
10	0/6	0/6	-	-

Table 2A : Acute Toxicity via the intravenous route in mice

LD_{50} (mg/kg)	L(-)- CA-10	L(-)- CA-12	L(-)- CA-14	L(-)- CA-16
	28.28	25.2	63.33	56.42
Dose (mg/kg)				
160	-	-	6/6	6/6
80	6/6	6/6	6/6	6/6
40	5/6	6/6	2/6	0/6
20	1/6	1/6	0/6	0/6
10	0/6	0/6	-	-

(1.3) Assessment of the irritating activity on the rabbit eye

The Federal Register test (vol. 38, 1973) modified as hereinbelow indicated was used.

Six New Zealand albino rabbits, weighing 1.5-2 kgs, were used for each test substance. Throughout the test the animals were caged so as to exclude possible extraneous materials that may produce eye irritation.

0.1 ml of a 1% solution of the test compounds was instilled with a dropper into the conjunctival sac of the rabbit right eye (the contralateral eye remained untreated and served as a control), whereupon the animals were caged again.

The treated eyes of all the animals were examined, in comparison with the control eye, 24, 48 and, if necessary, 72 hours following treatment.

The irritating activity was rated based on the scoring scale outlined in table 3.

The results are illustrated in table 4 and 4A.

Table 3:

Assessment of the irritating activity on the rabbit eye

Conjunctivae	
a) Conjestion	
- Vessels normal	0
- Vessels slightly injected	1
- Diffuse redness, vessels definetly injected not easily discernible	2
- Diffuse, beefy red	3
b) Chemosis	
- No oedema	0
- Slight oedema	1
- Severe oedema with eversion of lids	2
- Severe oedema with lids about half closed	3
- Severe oedema with lids more than half closed	4
Cornea	
- No alteration or opacity	0
- Scattered or confluent areas of opacity; details of iris visible	1
- Easily discernible translucent areas; details of iris slightly obscured	2
- Nacreous area: no details of iris visible; contours of pupil barely discernible	3
- Complete corneal opacity; iris not discernible	4
Iris	
- Normal	0
- Markedly deepened folds, more numerous than normal; congestion, swelling, moderate circum-corneal injection; iris still reacting to light	1
- No reaction to light; haemorrhage; gross destruction	2

Table 4: Assessment of the irritation activity on the rabbit eye

RABBIT No.	DL- CA-10 irritation score	DL- CA-12 irritation score	DL- CA-14 irritation score	DL- CA-16 irritation score
1	2	2	4	2
2	2	4	4	4
3	0	2	0	4
4	0	2	0	2
5	2	2	2	6
6	2	2	2	2
Average score	1.3	2.3	2.0	3.3

Table 4A : Assessment of the irritation activity on the rabbit eye

RABBIT No.	L(-)- CA-10 irritation score	L(-)- CA-12 irritation score	L(-)- CA-14 irritation score	L(-)- CA-16 irritation score
1	2	2	2	6
2	0	2	4	4
3	2	4	0	0
4	2	0	0	2
5	2	2	2	4
6	0	4	2	2
Average score	1.3	2.3	1.5	3

(1.4) Assessment of the cutaneous irritation activity in rabbits

Irritation to the skin was evaluated by the method illustrated in Federal Register (vol. 38, No. 187, page 27019, 1973) on albino rabbits weighing about 2 kgs.

Two days before the test was commenced, the back of th rabbits was clipped free of hair with an electric shearing machine, taking care not to bring about irritations and abrasions.

At test beginning, a zone of the skin was abraded by a sterile syringe needle.

Both on the intact and abraded skin an AL-test patch soaked in a 20% solution of the test compound was secured in place.

Similar patches (controls) soaked in the same volume of saline solution were secured in place on the intact and abraded skin.

The AL-test patches were secured in place to the animals by antiallergic adhesive plasters.

After 24 hours of exposures the patches were removed and the skin examined.

The reactions were evaluated at 24 and 72 hours on the basis of the table in Federal Register (see table 5). The results thus obtained are illustrated in table 6 and 6A.

Table 5:

Assessment of the cutaneous irritating activity

SKIN REACTIONS:	
1) ERYTHEMA	
No erythema	0
Slight barely perceptible erythema	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (intense redness) to slight eschar formation	4
2) OEDEMA	
No oedema	0
Slight, barely perceptible oedema	1
Slight oedema (with well-defined edges)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the exposure area)	4

The reaction value is the average of the values of six animals and is calculated by adding the values under 1) to the values under 2) for both intact and abraded skin. The resulting sum is divided by 24 and the result is termed "primary cutaneous irritation score".

The substance is regarded as:

non-irritating	if the score is 0
mildly irritating	if the score ranges between 0 and 2
averagely irritating	if the score ranges between 2 and 5
severely irritating	if the score ranges between 5 and 8

Table 6: Assessment of the cutaneous irritating activity

Rabbit	Skin	DL- CA-10 (*)					DL- CA-12 (**)				
		Erythema value after		Oedema value after		Total	Erythema value after		Oedema value after		Total
		24 hours	72 hours	24 hours	72 hours		24 hours	72 hours	24 hours	72 hours	
1	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
2	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
3	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
4	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
5	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
6	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
irritation score		0					1				

(*) Exposure period: 4 hours
(**) Exposure period: 24 hours

Table 6 (cont.): Assessment of the cutaneous irritating activity

Rabbit	Skin	DL- CA-14 (*)					DL- CA-16 (**)				
		Erythema value after		Oedema value after		Total	Erythema value after		Oedema value after		Total
		24 hours	72 hours	24 hours	72 hours		24 hours	72 hours	24 hours	72 hours	
1	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
2	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
3	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
4	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
5	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
6	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
irritation score		0					0				

(*) Exposure period: 24 hours
(**) Exposure period: 4 hours

Table 6A : Assessment of the cutaneous irritating activity

Rabbit	Skin	L(-)- CA-10 (*)					L(-)- CA-12 (**)				
		Erythema value after		Oedema value after		Total	Erythema value after		Oedema value after		Total
		24 hours	72 hours	24 hours	72 hours		24 hours	72 hours	24 hours	72 hours	
1	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
2	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
3	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
4	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
5	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
6	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
irritation score		0					1				

(*) Exposure period: 4 hours
(**) Exposure period: 24 hours

Table 6A (cont.): Assessment of the cutaneous irritating activity

Rabbit	Skin	L(-)- CA-14 (*)					L(-)- CA-16 (**)				
		Erythema value after		Oedema value after		Total	Erythema value after		Oedema value after		Total
		24 hours	72 hours	24 hours	72 hours		24 hours	72 hours	24 hours	72 hours	
1	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
2	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
3	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
4	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
5	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
6	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
irritation score		0					0				

(*) Exposure period: 24 hours
(**) Exposure period: 4 hours

ANTIBACTERIAL ACTIVITY

in vitro

1.1 Determination of antibacterial activity on Petri plates

The test was carried out on sterile Petri plates (14 cm of diameter), by inoculating the strains listed at point A in suitable culture media by the Kirby-Bauer method.

A)

1 - Bacillus subtilis ATCC 6633 on Müller Hinton agar
2 - Escherichia coli ATCC 25922 on Müller Hinton agar
3 - Staphylococcus aureus ATCC 6538 on Müller Hinton agar
4 - Mucor mucedo ATCC 7941 on Sabouraud maltose agar
5 - Candida albicans ATCC 2091 on Sabouraud maltose agar

The antibacterial activity of the compounds was evaluated by means of a well on the solidified medium. The results are shown in table 7 and 7A.

Table 7: Antibacterial Activity (diameter in mm)

Concentration	(DL) Compound	E. coli	Staph. aureus	Bac. subtilis	Cand. albic.	Mucor mucedo (*)
0,1%	C10	10.7	10.8	14.0	12.7	+ -
	C12	19.1	16.9	18.0	17.3	+ +
	C14	10.6	10.3	10.9	13.4	+ -
	C16	10.4	10.6	9.9	13.5	+
1%	C10	14.1	14.6	27.1	24.0	+ +
	C12	28.6	19.8	23.0	24.8	+ + +
	C14	12.7	13.0	12.4	16.8	+ -
	C16	11.0	12.4	11.0	14.7	+
10%	C12	30.6	21.8	27.0	25.0	+ + +
	C14	15.4	18.1	17.0	17.9	+ -
	C16	11.4	16.1	14.6	16.0	+
	DL-carnitinamide-chloride	-	-	-	-	-

(*) +- = 10.0 to 12.0 mm in diameter
+ = 12.0 to 19.0 mm in diameter
++ = 19.0 to 29.0 mm in diameter
+++ = 29.0 to 35.0 mm in diameter

Table 7A : Antibacterial Activity (diameter in mm)

Concentration	L(-) Compound	E. coli	Staph. aureus	Bac. subtilis	Cand. albic.	Mucor mucedo (*)
0,1%	C10	10.8	11.5	13.0	12.3	+ -
	C12	20.7	15.6	19.0	18.2	+ +
	C14	10.6	11.4	10.1	13.8	+ -
	C16	10.9	10.6	9.6	12.0	+
1%	C10	14.8	15.3	24.1	21.0	+ +
	C12	28.8	18.8	26.0	23.9	+ + +
	C14	11.0	14.1	12.9	16.1	+
	C16	10.6	13.2	11.5	13.0	+
10%	C12	30.6	20.5	27.9	24.8	+ + +
	C14	16.3	19.6	18.1	19.3	+
	C16	11.5	15.9	13.6	16.4	+
	DL-carnitinamide-chloride	-	-	-	-	-

(*) +- = 10.0 to 12.0 mm in diameter
+ = 12.0 to 19.0 mm in diameter
++ = 19.0 to 29.0 mm in diameter
+++ = 29.0 to 35.0 mm in diameter

in vitro

2.1 Determination of Minimum Inhibiting Concentration (MIC)

The test was carried out on sterile Petri dishes (10 cm of diameter) loaded with 10 ml of medium and antibacterial substance at given concentration, mixed at 9:1 ratio.

The medium used was

(1) Müller Hinton agar for bacteria, and

(2) Sabouraud Dextrose agar for fungi

The solidified plates were then inoculated at the surface thereof with a multi-point inoculator equipped with 48 rods, each of which had been coated with a suspension of the tested microorganism. The suspensions were prepared with the Kirby-Bauer method (Bauer, Kirby, Sherris, Turck 1966, Am. J. Clin. Pathol. 45:49-496) modified according to D'Amato-Hochstein (D'Amato-Hochstein, 1982, J. Clin. Microb. 15 (2) 282-285).

The inoculated plates were incubated at 35 °C (culture medium (1)) and 25 °C (culture medium (2)) respectively.

Reading was carried out after 15-18 hours for bacteria and after 24-30 hours for fungi.

MIC values thus obtained are shown in table 8 and 8A.

Table 8: Minimum Inhibiting Concentration (mcg)

Method: Petri dishes with solid culture medium

		DL- CA-10	DL- CA-12	DL- CA-14	DL- CA-16
Staphylococcus aureus	10547	62	15	15	15
"	8530	62	31	15	15
"	6538P	31	62	250	> 500
"	80R	62	15	15	15
"	58R	62	62	31	31
Enterococcus	1 Renz.	62	7	< 7	< 7
"	2 Renz.	62	7	< 7	< 7
Strept. faecalis lactis R	8043	62	< 7	< 15	< 7
" " "	66/48	62	7	< 7	< 7
" faecium	UM	31	< 7	< 7	< 7
Sarcina lutea	9341	250	62	62	15
Bacillus subtilis	6633	62	15	15	31
Pseudomonas aeruginosa	3E	> 500	250	> 500	> 500
" "	50F	> 500	250	> 500	> 500
" "	12F	> 500	125	> 500	> 500
Salmonella typhi	SK	125	62	250	> 500
Salmonella typhi	6539	62	31	15	31

Table 8 (cont.): Minimum Inhibiting Concentration (mcg)

Method: P tri dishes with solid culture medium

		DL- CA-10	DL- CA-12	DL- CA-14	DL- CA-16
Enterobacter cloacae	P99 β-Latt.	250	31	125	>500
Shigella sonnei	SK	125	62	200	>500
Escherichia coli	4	125	62	250	>500
" "	828	500	125	>500	>500
" "	92F	250	62	250	>500
" "	66/46	125	62	>500	>500
" "	R57B	250	125	>500	500
Klebsiella pneumoniae	IB 1 (pat.)	500	31	250	500
Candida albicans	A 215	250	62	15	125
" "	i6	250	62	15	62
" "	ISS 562	250	62	15	62
Candida tropicalis	ISS 5705	250	< 7	31	7
Mucor Mucedo	7941	250	15	15	62
Aspergillus niger	9642	500	15	15	15

Table 8A : Minimum Inhibiting Concentration (mcg)

Method: Petri dishes with solid culture medium

		L(-)- CA-10	L(-)- CA-12	L(-)- CA-14	L(-)- CA-16
Staphylococcus aureus	10547	31	15	15	15
"	8530	31	31	62	15
"	6538P	62	62	250	> 500
"	80R	62	15	15	15
"	58R	62	15	15	15
Enterococcus	1 Renz.	62	7	15	< 7
"	2 Renz.	62	7	< 7	< 7
Strept. faecalis lactis R	8043	62	< 7	< 7	15
" " "	66/48	62	7	< 7	< 7
" faecium	UH	31	< 7	< 7	< 7
Sarcina lutea	9341	125	62	62	31
Bacillus subtilis	6633	62	15	15	31
Pseudomonas aeruginosa	3E	> 500	250	> 500	> 500
" "	50F	> 500	62	> 500	> 500
" "	12F	> 500	125	> 500	> 500
Salmonella typhi	SK	125	62	250	250
Salmonella typhi	6539	62	31	15	31

Table 8A (c nt.): Minimum Inhibiting Concentration (mcg)

Method: Petri dish s with solid culture medium

		L(-)- CA-10	L(-)- CA-12	L(-)- CA-14	L(-)- CA-16
Enterobacter cloacae	P99 β-Latt.	125	62	125	>500
Shigella sonnei	SK	125	62	200	>500
Escherichia coli	4	125	62	250	>500
" "	828	250	125	>500	>500
" "	92F	500	62	500	>500
" "	66/46	125	125	>500	>500
" "	R57B	500	250	>500	>500
Klebsiella pneumoniae	IB 1 (pat.)	500	62	250	>500
Candida albicans	A 215	250	62	15	125
" "	i6	250	62	15	62
" "	ISS 562	250	31	31	31
Candida tropicalis	ISS 5705	250	< 7	31	15
Mucor Mucedo	7941	250	15	15	62
Aspergillus niger	9642	500	15	31	15

ANTIDANDRUFF ACTIVITY

in vitro

3.1 DL and L(-) CA-12 activity on Pityrosporum ovalis ATCC 12078

The test was carried out on sterile Petri plates having 10 cm of diameter filled with 10 ml of medium inoculated with the tested microorganism.

Sabouraud maltose agar + 1% Tween 80 was used as culture medium.

The Kirby-Bauer method modified according to D'Amato-Hochstein was used.

The plates after inoculation by means of wells on the agar-containing medium were incubated at 35 °C for 48 hours.

The diameter of the growth inhibition zone was 20.3 mm for the 1% DL solution and 20.5 mm for the 1% L(-) solution and 9.91 mm for the 0.1% DL solution and 10.2 for the 0.1% L(-) solution.

3.2 Minimum inhibiting concentration of DL and L(-) CA-12 on Pityrosporum ovalis ATCC 12078

The test was carried out following the method outlined at point 2.1, except that the medium was modified by the addition of 1% Tween 80. The resulting MIC was 50 mcg for both DL and L(-).

The compounds of the invention are suitable for being compounded into pharmaceutical, cosmetic and over-the-counter (OTC) compositions, such as mouthwashes, external disinfectants, deodorants, shaving creams an the like. It was found that, generally, the optimum concentration of N-alkylamides of formula (I) in the compositions is 0.1-0.3% by weight for a preservative action and 0.3-1% by weight for a disinfectant action.

Some compositions according to the invention are hereinbelow indicated.

Alcoholic deodorant

Ethanol	42 g
Perfume	0.1 g
DL or L(-) CA-12	0.1 g
Propylene glycol	3 g
Softigen 767	0.5 g
Deionized water	balance to 100 g

Alcohol-free deodorant

Ethanol	3 g
Solulan C 24	1 g
Perfume	0.1 g
Propylene glycol	3 g
DL or L(-) CA-12	0.1 g
Lanidrol (lanolin alcohol)	0.5 g
Deionized water	balance to 100 g

Shaving cream

Esso wax 5250	6 g
Marcol 52	6.5 g
Laurex CS	10 g
Tween 60	3 g

Silicone oil AK 350	1 g
Butylhydroxyanisole	0.05 g
Steinamid P256	1.7 g
DL or L(-) CA-12	0.15 g
EDTA (ethylenediaminetetraacetic acid)	0.2 g
Propylene glycol	3 g
Empigen BT	5 g
Polimer JR 400	0.1 g
Perfume	0.35 g
Deionized water	balance to 100 g

Liquid detergent

Empilan 2574	1 g
Tween 20	2.4 g
Tween 80	1.5 g
Empigen BT	40 g
Zetesol 250	7.6 g
Neo extrapon lemon	0.1 g
Sigma antioxidant	0.1 g
EDTA	0.1 g
DL or L(-) CA-12	0.15 g
Solulan 16	0.6 g
Phosphoric acid	0.12 g
Coconut oil diethanolamide	3 g
Deionized water	balance to 100 g

Chewing gum

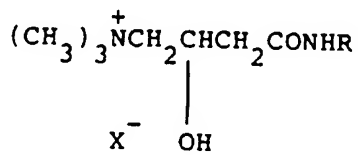
Chlorofil	0.0027 g
Sodium fluoride	0.0152 g
DL or L(-) CA-12	0.667 g
Micronized sorbitol	35.78 g
Micronized mannitol	13.55 g
Gum base	28.74 g

Aroma	0.282	g
Menthol	0.406	g
70% sorbitol solution	17.35	g

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, LI, LU, NL, SE

1. N-alkylamides of DL and L(-)-carnitine having general formula (I)



(I)

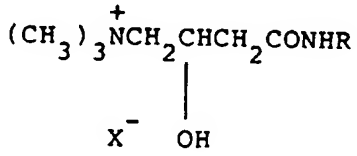
wherein :

X^- is OH^- or the anion of a pharmacologically acceptable acid, and

R is a straight C_{10}-C_{16} alkyl radical.

2. N-alkylamides of DL and L(-)-carnitine according to claim 1, wherein X^- is Cl^-.

3. A process for preparing N-alkylamides of DL and L(-)-carnitine having general formula (I)



(I)

wherein :

X^- is OH^- or the anion of a pharmacologically acceptable acid, and

R is a straight C_{10}-C_{16} alkyl radical

which comprises the steps of

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}-C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120-140 °C, for 2-4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture a mixture of DL or L(-)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of DL or L(-)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110-130 °C for about 34-38 hours in an atmosphere of inert gas.

4. The process of claim 3, wherein the high-boiling solvent is ethylene glycol.

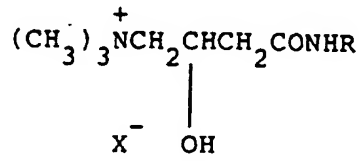
5. A composition suitable for topical application having antibacterial activity which comprises an amount effective for exerting a disinfectant action of at least one of the N-alkylamides of DL and L(-)-carnitine of claim 1.

6. The composition of claim 5 comprising about 0.3-1.0% by weight of one of the N-alkylamides of DL and L(-)-carnitine of claim 1.

7. The composition of claim 5 or 6 in the form of a mouthwash, external disinfectant, deodorant, face cream, body cream and shaving cream.

Claims for the following Contracting State: ES

1. A process for preparing N-alkylamides of DL and L(-)-carnitine having general formula (I)



(I)

wherein :

X^- is OH^- or the anion of a physiologically acceptable acid, and

R is a straight C_{10}-C_{16} alkyl radical

which comprises the steps of

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}-C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120-140 °C, for 2-4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture a mixture of DL or L(-)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of DL or L(-)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110-130 °C for about 34-38 hours in an atmosphere of inert gas.

2. The process of claim 1, wherein the high-boiling solvent is ethylene glycol.

3. Application of the N-alkylamides of DL and L(-)-carnitine obtained with the process according to claim 1 or 2 to the preparation of cosmetic compositions.

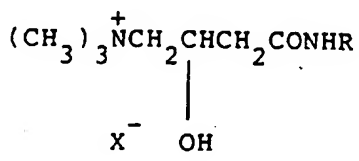
4. A cosmetic composition suitable for topical application which comprises at least one of the N-alkylamides of DL and L(-)-carnitine obtained with the process according to claim 1 or 2.

5. The composition of claim 4 comprising about 0.3-1.0% by weight of one of the N-alkylamides of DL and L(-)-carnitine obtained with the process according to claim 1 or 2.

6. The composition of claim 4 or 5 in the form of a deodorant, face cream, body cream and shaving cream.

Claims for the following Contracting State: GR

1. N-alkylamides of DL and L(-)-carnitine having general formula (I)



(I)

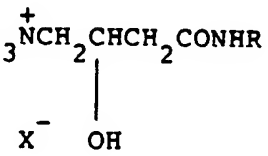
wherein :

X^- is OH^- or the anion of a physiologically acceptable acid, and

R is a straight C_{10}-C_{16} alkyl radical.

2. N-alkylamides of DL and L(-)-carnitine according to claim 1, wherein X^- is Cl^-.

3. A process for preparing N-alkylamides of DL and L(-)-carnitine having general formula (I)



(I)

wherein :

X^- is OH^- or the anion of a pharmacologically acceptable acid, and

R is a straight C_{10}-C_{16} alkyl radical

which comprises the steps of

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}-C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120-140 °C, for 2-4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture a mixture of DL or L(-)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of DL or L(-)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110-130 °C for about 34-38 hours in an atmosphere of inert gas.

4. The process of claim 3, wherein the high-boiling solvent is ethylene glycol.

5. Application of the N-alkylamides of DL and L(-)-carnitine of claim 1 to the preparation of cosmetic compositions.

6. A cosmetic composition suitable for topical application which comprises at least one of the N-alkylamides of DL and L(-)-carnitine of claim 1.

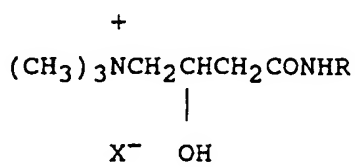
7. The composition of claim 6 comprising about 0.3-1.0% by weight of one of the N-alkylamides of DL and L(-)-carnitine of claim 1.

8. The composition of claim 6 or 7 in the form of a deodorant, face cream, body cream and shaving cream.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, LI, LU, NL, SE

1. N-Alkylamide von D,L- und L(-)-Carnitin der allgemeinen Formel (I)

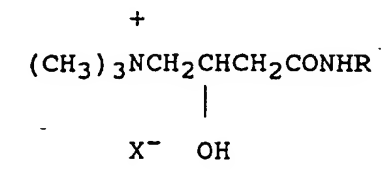


(I)

worin X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und R ein geradkettiger C_{10-16}-Alkylrest ist.

2. N-Alkylamide von D,L- und L(-)-Carnitin gemäss Anspruch 1, worin X^- Cl^- ist.

3. Verfahren zur Herstellung von N-Alkylamiden von D,L- und L(-)-Carnitin der allgemeinen Formel (I)



(I)

worin X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und R ein geradkettiger C_{10-16}-Alkylrest ist, welches die Stufen umfasst:

(a) Umsetzen eines Alkylamins der Formel NH_2R, worin R ein geradkettiger C_{10-16}-Alkylrest ist, mit einer im wesentlichen äquimolaren Menge von H_3PO_4 bei 120 bis 140 °C während 2 bis 4 Stunden in einer Inertgasatmosphäre in Gegenwart eines hochsiedenden Lösungsmittels; und

(b) Zugabe zu dem Reaktionssgemisch einer Mischung von D,L- oder L(-)-Carnitinamid-chlorid und Alkylamin NH_2R in einem Molverhältnis von etwa 1:1,1, wobei das Molverhältnis von D,L- oder L(-)-Carnitinamid-chlorid etwa zweimal der molaren Menge von H_3PO_4 entspricht, und wobei man die erhaltene Reaktionsmischung bei etwa 110 bis 130 °C während etwa 34 bis 38 Stunden in einer Inertgasatmosphäre rührt.

4. Verfahren gemäss Anspruch 3, bei dem das hochsiedende Lösungsmittel Ethylenglykol ist.

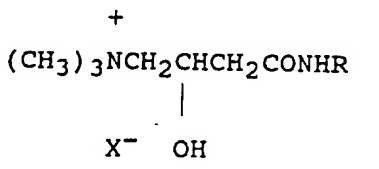
5. Zusammensetzung, die für die topische Anwendung mit antibakterieller Wirksamkeit geeignet ist, umfassend eine zur Ausübung einer Desinfektionswirkung wirksame Menge wenigstens eines der N-Alkylamide von D,L- und L(-)-Carnitin gemäss Anspruch 1.

6. Zusammensetzung gemäss Anspruch 5, umfassend etwa 0,3 bis 1,0 Gew.% eines der N-Alkylamide von D,L- und L(-)-Carnitin gemäss Anspruch 1.

7. Zusammensetzung gemäss Ansprüchen 5 oder 6 in Form eines Mundwassers, äusseren Desinfektionsmittels, Deodorants, einer Gesichtscreme, einer Körpercreme und einer Rasiercreme.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung von N-Alkylamiden von D,L- und L(-)-Carnitin der allgemeinen Formel (I)



(I)

worin X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und R ein geradkettiger C_{10-16}-Alkylrest ist, welches die Stufen umfasst:

(a) Umsetzen eines Alkylamins der Formel NH_2R, worin R ein geradkettiger C_{10-16}-Alkylrest ist, mit einer im wesentlichen äquimolaren Menge von H_3PO_4 bei 120 bis 140 °C während 2 bis 4 Stunden in einer Inertgasatmosphäre in Gegenwart eines hochsiedenden Lösungsmittels; und

(b) Zugabe zu dem Reaktionssgemisch einer Mischung von D,L- oder L(-)-Carnitinamid-chlorid und Alkylamin NH_2R in einem Molverhältnis von etwa 1:1,1, wobei das Molverhältnis von D,L- oder L(-)-Carnitinamid-chlorid etwa zweimal der molaren Menge von H_3PO_4 entspricht, und wobei man die erhaltene Reaktionsmischung bei etwa 110 bis 130 °C während etwa 34 bis 38 Stunden in einer Inertgasatmosphäre rührt.

2. Verfahren gemäss Anspruch 1, bei dem das hochsiedende Lösungsmittel Ethylenglykol ist.

3. Anwendung von N-Alkylamiden von D,L- und L(-)-Carnitin, erhalten nach dem Verfahren gemäss Ansprüchen 1 oder 2, für die Herstellung von kosmetischen Zusammensetzungen.

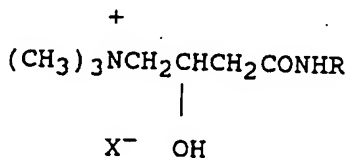
4. Kosmetische Zusammensetzung, die für die topische Anwendung geeignet ist, umfassend wenigstens eines der N-Alkylamide von D,L- und L(-)-Carnitin, erhalten nach dem Verfahren gemäss Ansprüchen 1 oder 2.

5. Zusammensetzung gemäss Anspruch 4, umfassend etwa 0,3 bis 1,0 Gew.% eines der N-Alkylamide von D,L-und L(-)-Carnitin, erhalten nach dem Verfahren gemäss Ansprüchen 1 oder 2.

6. Zusammensetzung gemäss Ansprüchen 4 oder 5 in Form eines Deodorants, einer Gesichtscreme, einer Körpercreme und einer Rasiercreme.

Patentansprüche für folgenden Vertragsstaat : GR

1. N-Alkylamide von D,L- und L(-)-Carnitin der allgemeinen Formel (I)

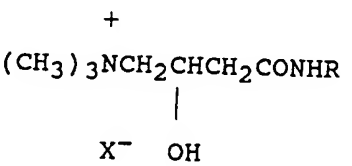


(I)

worin X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und R ein geradkettiger C_{10-16}-Alkylrest ist.

2. N-Alkylamide von D,L- und L(-)-Carnitin gemäss Anspruch 1, worin X^- Cl^- ist.

3. Verfahren zur Herstellung von N-Alkylamiden von D,L- und L(-)-Carnitin der allgemeinen Formel (I)



(I)

worin X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und R ein geradkettiger C_{10-16}-Alkylrest ist, welches die Stufen umfasst:

(a) Umsetzen eines Alkylamins der Formel NH_2R, worin R ein geradkettiger C_{10-16}-Alkylrest ist, mit einer im wesentlichen äquimolaren Menge von H_3PO_4 bei 120 bis 140 °C während 2 bis 4 Stunden in einer Inertgasatmosphäre in Gegenwart eines hochsiedenden Lösungsmittels; und

(b) Zugabe zu dem Reaktionssgemisch einer Mischung von D,L- oder L(-)-Carnitinamid-chlorid und Alkylamin NH_2R in einem Molverhältnis von etwa 1:1,1, wobei das Molverhältnis von D,L- oder L(-)-Carnitinamid-chlorid etwa zweimal der molaren Menge von H_3PO_4 entspricht, und wobei man die erhaltene Reaktionsmischung bei etwa 110 bis 130 °C während etwa 34 bis 38 Stunden in einer Inertgasatmosphäre rührt.

4. Verfahren gemäss Anspruch 3, bei dem das hochsiedende Lösungsmittel Ethylenglykol ist.

5. Anwendung von N-Alkylamiden von D,L- und L(-)-Carnitin gemäss Anspruch 1 zur Herstellung von kosmetischen Zusammensetzungen.

6. Kosmetische Zusammensetzung, die für die topische Anwendung geeignet ist, umfassend wenigstens eines der N-Alkylamide von D,L- und L(-)-Carnitin gemäss Anspruch 1.

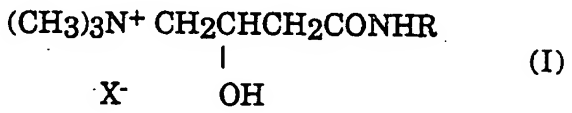
7. Zusammensetzung gemäss Anspruch 6, umfassend etwa 0,3 bis 1,0 Gew.% eines der N-Alkylamide von D,L-und L(-)-Carnitin gemäss Anspruch 1.

8. Zusammensetzung gemäss Ansprüchen 6 oder 7 in Form eines Deodorants, einer Gesichtscreme, einer Körpercreme und einer Rasiercreme.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, LI, LU, NL, SE

1. N-alkylamides de D,L et de L(-)-carnitine, ayant la formule générale (I) :

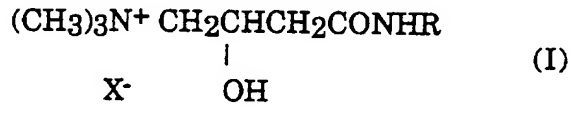


(I)

dans laquelle:
X^- est OH^- ou l'anion d'un acide acceptable du point de vue pharmaceutique et
R est un radical alkyle en C_{10-16} à chaîne droite.

2. N-alkylamides de D,L et de L(-)-carnitine suivant la revendication 1, dans lesquels X^- est Cl^-.

3. Procédé de préparation de N-alkylamides de D,L et de L(-)-carnitine, ayant la formule générale (I) :



(I)

dans laquelle:
X^- est OH^- ou l'anion d'un acide acceptable du point de vue pharmaceutique et
R est un radical alkyle en C_{10-16} à chaîne droite,
qui comprend les étapes suivantes:
(a) réaction d'une alkylamine de formule NH_2R dans laquelle R est un radical alkyle en C_{10-16} à chaîne droite avec une quantité pratiquement équimolaire de H_3PO_4, à 120-140 °C pendant 2 à 4 heures, dans une atmosphère de gaz inerte, en présence d'un solvant à point d'ébullition élevé; et
(b) addition au mélange réactionnel d'un mélange de chlorure de D,L ou de L(-)-carnitinamide et d'alkylamine NH_2R selon un rapport molaire d'environ 1/1,1, la quantité molaire du chlorure de D,L ou de L(-)-carnitinamide étant environ deux fois la quantité molaire de H_3PO_4 et agitation du mélange réactionnel résultant à environ 110-130 °C pendant environ 34 à 38 heures sous atmosphère de gaz inerte.

4. Procédé suivant la revendication 3, dans lequel le solvant à haut point d'ébullition est l'éthylène glycol.

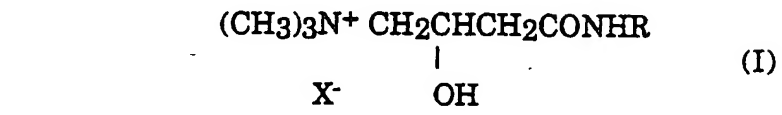
5. Composition convenable pour l'application topique ayant une activité antibactérienne, qui comprend une quantité efficace pour exercer une action désinfectante d'au moins l'un des N-alkylamides de D,L et de L(-)-carnitine suivant la revendication 1.

6. Composition suivant la revendication 5, comprenant d'environ 0,3 à 1,0% en poids de l'un des N-alkylamides de D,L et de L(-)-carnitine suivant la revendication 1.

7. Composition suivant la revendication 5 ou la revendication 6, sous la forme d'eau dentifrice, de désinfectant externe, de déodorant, de crème pour le visage, de crème pour le corps et de crème à raser.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation de N-alkylamides de D,L et de L(-)-carnitine, ayant la formule générale (I) :



(I)

dans laquelle:
X^- est OH^- ou l'anion d'un acide acceptable du point de vue pharmaceutique et
R est un radical alkyle en C_{10-16} à chaîne droite,
qui comprend les étapes suivantes:
(a) réaction d'une alkylamine de formule NH_2R dans laquelle R est un radical alkyle en C_{10-16} à chaîne droite avec une quantité pratiquement équimolaire de H_3PO_4, à 120-140 °C pendant 2 à 4 heures, dans une atmosphère de gaz inerte, en présence d'un solvant à point d'ébullition élevé; et
(b) addition au mélange réactionnel d'un mélange de chlorure de D,L ou de L(-)-carnitinamide et d'alkylamine NH_2R selon un rapport molaire d'environ 1/1,1, la quantité molaire du chlorure de D,L ou de L(-)-carnitinamide étant environ deux fois la quantité molaire de H_3PO_4 et agitation du mélange réactionnel résultant à environ 110-130 °C pendant environ 34 à 38 heures sous atmosphère de gaz inerte.

2. Procédé suivant la revendication 1, dans lequel le solvant à haut point d'ébullition est l'éthylène glycol.

3. Application des N-alkylamides de D,L et de L(-)-carnitine obtenus avec le procédé suivant la revendication 1 ou la revendication 2, à la préparation de compositions cosmétiques.

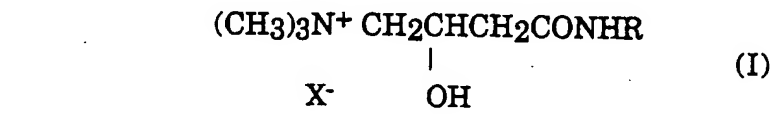
4. Composition convenable pour l'application topique ayant une activité antibactérienne, qui comprend au moins l'un des N-alkylamides de D,L et de L(-)-carnitine obtenus avec le procédé suivant la revendication 1 ou la revendication 2.

5. Composition suivant la revendication 4, comprenant d'environ 0,3 à 1,0% en poids de l'un des N-alkylamides de D,L et de L(-)-carnitine obtenus avec le procédé suivant la revendication 1 ou la revendication 2.

6. Composition suivant la revendication 4 ou la revendication 5, sous la forme de déodorant, de crème pour le visage, de crème pour le corps et de crème à raser.

Revendications pour l'Etat contractant suivant : GR

1. N-alkylamides de D,L et de L(-)-carnitine, ayant la formule générale (I) :



(I)

dans laquelle:
X^- est OH^- ou l'anion d'un acide acceptable du point de vue pharmaceutique et
R est un radical alkyle en C_{10-16} à chaîne droite.

2. N-alkylamides de D,L et de L(-)-carnitine suivant la revendication 1, dans lesquels X^- est Cl^-.

3. Procédé de préparation de N-alkylamides de D,L et de L(-)-carnitine, ayant la formule générale (I) :

$$\underset{X^-}{(CH_3)_3N^+}\,CH_2\underset{OH}{\underset{|}{C}}HCH_2CONHR \qquad (I)$$

dans laquelle:

X^- est OH^- ou l'anion d'un acide acceptable du point de vue pharmaceutique et
R est un radical alkyle en C_{10-16} à chaîne droite,

qui comprend les étapes suivantes:

(a) réaction d'une alkylamine de formule NH_2R dans laquelle R est un radical alkyle en C_{10-16} à chaîne droite avec une quantité pratiquement équimolaire de H_3PO_4, à 120-140 °C pendant 2 à 4 heures, dans une atmosphère de gaz inerte, en présence d'un solvant à point d'ébullition élevé; et
(b) addition au mélange réactionnel d'un mélange de chlorure de D,L ou de L(-)-carnitinamide et d'alkylamine NH_2R selon un rapport molaire d'environ 1/1,1, la quantité molaire du chlorure de D,L ou de L(-)-carnitinamide étant environ deux fois la quantité molaire de H_3PO_4 et agitation du mélange réactionnel résultant à environ 110-130 °C pendant environ 34 à 38 heures sous atmosphère de gaz inerte.

4. Procédé suivant la revendication 3, dans lequel le solvant à haut point d'ébullition est l'éthylène glycol.

5. Application des N-alkylamides de D,L et de L(-)-carnitine suivant la revendication 1 à la préparation de compositions cosmétiques.

6. Composition cosmétique convenable pour l'application topique, qui comprend au moins l'un des N-alkylamides de D,L et de L(-)-carnitine suivant la revendication 1.

7. Composition suivant la revendication 6, comprenant d'environ 0,3 à 1,0% en poids de l'un des N-alkylamides de D,L et de L(-)-carnitine suivant la revendication 1.

8. Composition suivant la revendication 6 ou la revendication 7, sous la forme de déodorant, de crème pour le visage, de crème pour le corps et de crème à raser.